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Mercury: Major Issues in Environmental Health

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In the past, methylmercury compounds were manufactured as fungicides or appeared as unwanted byproducts of the chemical industry, but today the methylation of inorganic mercury in aquatic sediments and soils is the predominant if not the sole source of methylmercury. This form of mercury is bioaccumulated to a high degree in aquatic food chains to attain its highest concentrations in edible tissues in long-lived predatory fish living in both fresh and ocean waters. It is well absorbed from the diet and distributes within a few days to all tissues in the body. It crosses without hindrance the blood–brain and placental barriers to reach its principal target tissue, the brain. It is eliminated chiefly in the feces after conversion to inorganic mercury. The biological half-time of methylmercury in human tissues is about 50 days, but there is wide individual variation. Adult poisoning is characterized by focal damage to discrete anatomical areas of the brain such as the visual cortex and granule layer of the cerebellum. A latent period of weeks or months may ensue before the appearance of signs and symptoms of poisoning. The latter manifest themselves as paresthesia, ataxia, constriction of the visual fields, and hearing loss. The prenatal period is the most sensitive stage of the life cycle to methylmercury. Prenatally poisoned infants exhibit a range of effects from severe cerebral palsy to subtle developmental delays. Methylmercury is believed to inhibit those processes in the brain specially involved in development and growth such as neuronal cell division and migration.

Introduction

Early in David Rall's tenure as Director of the National Institute of Environmental Health Sciences, methylmercury attracted public attention as an environmental human health threat. Rall responded by sponsoring research via both his extramural and intramural programs. In the late 1960s, methylmercury attracted attention as a potent environmental threat to human health. An acetaldehyde manufacturing factory in Minamata, Japan, used inorganic mercury salts as catalysts. Some of the mercury was chemically converted to methylmercury compounds, released in waste waters into a large ocean bay (Minaata Bay, Japan), and let to devastating consequences to fishermen, their families, and fish consumers in that area. This outbreak in the 1950s illustrated a unique property of methylmercury—that it could be released into ocean water and return in such high concentrations in fish tissues as to cause widespread human fatalities. We now know that the bioaccumulation factor from water to edible fish tissue exceeds 10 million for certain species of fresh and ocean water fish.

The potential of methylmercury for ecological damage was illustrated by reports of devastated bird populations in the 1960s (*1*). Methylmercury compounds had been used as fungicides on seed grain both in Europe and North America. As fungicides they were ecnomical and highly effective in suppressing cereal infections such as "bunt" disease and in this way greatly increased crop yields. However, the seeds were consumed by birds and small mammals who in turn were part of the food chain for predatory birds. It was the discovery of the poisoning of large birds such as eagles, hawks, and owls that led to the identification of the role of methylmercury as an ecological poison.

The agricultural use of methylmercury fungicides has also taken its toll on human health. Several outbreaks occurred during the 1960s in developing countries due to the misuse of methyl and ethylmercury fungicides (*2*). Farmers and their families, instead of using the fungicide-treated grain for planting, used it for homemade bread. These outbreaks culminated in the most serious episode in the winter of 1971–1972 in rural Iraq. More than 6000 cases of severe poisoning and more than 600 deaths were recorded in hospitals throughout the country (*3*). Morbidity and mortality outside the hospital may have been much higher (*4*).

To date, all these outbreaks have been characterized by the use or accidental release of "man-made" methylmercury compounds. In one of the most surprising environmental findings of this century, it was discovered that fish caught in waters where no methylmercury had been released had high methylmercury levels in their tissues. Subsequently, Jensen and Jernelov (*5*) in Sweden and Wood et al. (*6*) in the United States demonstrated that certain classes of microorganisms were capable of methylating inorganic mercury to mono- and dimethylmercury compounds. This finding explained the presence of methylmercury in wide-ranging ocean fish and in freshwater fish caught in areas where only inorganic mercury had been released or where geologic sources of inorganic mercury were present.

Thus, by the early 1970s it was clear that methylmercury was not only an environmental hazard from anthropogenic uses but also from uses of inorganic mercury and even from the methyla-

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tion of geological mercury. There was an urgent need to assess the public health risk from methylmercury in fish and to understand the toxicology of the form of mercury. The National Institute of Environmental Health Sciences, therefore, promoted research into the human health and toxicological aspects.

Other agencies promoted studies into the environmental fate of mercury. Such studies are outside the scope of this article. However, as background to the human health risks, I will first summarize the findings dealing with pathways of human exposure.

Pathways of Human Exposure to Methylmercury

Mercury exists in a large number of physical and chemical states, some of which play an important role in the environmental fate of this element. Mercury vapor, Hg^0,is a monatomic gas, stable at room temperatures. It is by far the principal form in the earth's atmosphere. The sources are degassing from the earth's crust and especially volcanic activity (*7*). Emissions related to human activity may account for up to half the total emissions and are due to the burning of fossil fuels, smelting metal ores, mercury mining, and waste incinerators and crematories. Its residence time in the atmosphere is measured in months or years so that, once released into the atmosphere, mercury vapor is globally distributed.

The pathways of return to the earth's surface are not well understood but may be of great importance in determining mercury levels in fish (*8*). It is believed that mercury vapor is converted to water-soluble forms, presumably by oxidation to divalent inorganic mercury, Hg^{2+}, and deposited back to the earth's surface in rain water. Both abiotic and biotic mechanisms in soil and water can reduce Hg^{2+} back to Hg^0 and thereby return mercury to the atmosphere.

Mercury deposited to surface water as well as mercury present in bottom sediments is subject to methylation by microorganisms (*9*). Methylmercury enters aquatic food chains, starting with uptake into small organisms such as plankton and eventually attaining its highest concentration in large, predatory fish. Methylmercury is poorly, if at all, eliminated from fish so that it accumulates throughout the lifetime of the fish. Thus the highest concentrations are found in the longest lived, top predatory fish such as shark and swordfish in the oceans and pike and bass in freshwater.

Several other factors affect methylmercury levels in fish. Acidification of bodies of freshwater by acid rain results in higher levels of methylmercury in fish. Recent studies suggest that a lower pH favors methylating over demethylation reactions in water and sediments (*10*). The impounding of rivers and lakes to produce hydroelectric power also raises methylmercury levels in fish. The mechanism is poorly understood, but it has been suggested that the flooding of vegetation results in enhanced substrate supply to microorganisms, including those species that methylate mercury (*10*). The raising and lowering of water levels in response to electric power demands causes further erosion of the banks of impounded lakes and rivers and the deposition of more vegetation into the water.

The long-distance atmospheric transport of mercury, and in certain areas, the effects of acid rain and water impoundment, have led to thousands of lakes in North America being "blacklisted" because the fish exceed state or Federal health guidelines for methylmercury. Overt cases of poisoning from fish containing "naturally" methylated mercury have not been reported. However, populations dependent on fish as a major source of protein have developed blood levels of methylmercury that overlap the lowest levels associated with symptoms of mercury poisoning in the outbreaks in Japan and Iraq.

Because methylmercury compounds are no longer used as fungicides, the principal and probably sole route of human exposure is through consumption of fish and fish products. In the case of Inuit populations in North America, and in northern island communities such as the Faroe Islands (*11*), consumption of marine mammals would also be an important route. To control human consumption of methylmercury regulatory agencies, have set limits on concentrations in fish. The scientific basis for this procedure is indicated in Figure 1. Measurements of methylmercury in edible tissues of fish, along with dietary information on fish intake, allow estimates of human intake of metlylmercury, not only the average intake but more importantly the range of human intake. Pharmacokinetic models are used to estimate the predicted levels in indicator media such as blood for any given daily intake of methylmercury. Thus a range of daily intakes may be converted to a range of levels in blood or other indicator media.

Dose–response relationships that compare levels in indicator media to frequency of observed toxic effects in humans are used to estimate the risk to a population having a specified range of daily intakes (Fig. 1). If the fraction of the population at risk is deemed too high, the regulatory agency will reduce the allowable levels in fish to a value giving an acceptable risk to the population. The NIEHS has supported a great deal of research into estimates of human intake and dose–response relationships both in the quantitative characterization in humans and in the underlying mechanisms.

Disposition of Methylmercury

Early studies on animals indicated that methylmercury compounds added to the diet were virtually completely absorbed (*12*). Similar findings were reported from an experimental test in human volunteers in a study in Finland (*13*). Our observations on blood levels in subjects ingesting known amounts of methylmercury in fish were consistent with a high efficiency of absorption [more than 90% of the ingested amount (*14*)].

Methylmercury distributes to all regions of the body. The study by Kershaw et al. (*14*) showed that distribution to the blood compartment was complete in about 30 hr and accounted for 7% of the ingested dose. Earlier work in Sweden using radiolabeled methylmercury indicated that distribution to the brain took longer, about 3 days (*15*).

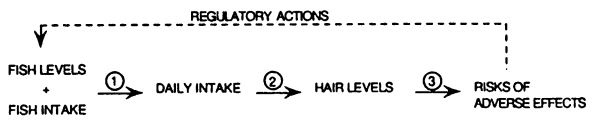

FIGURE 1. A diagrammatic representation of the scientific basis for setting regulatory guidelines for methylmercury in fish.

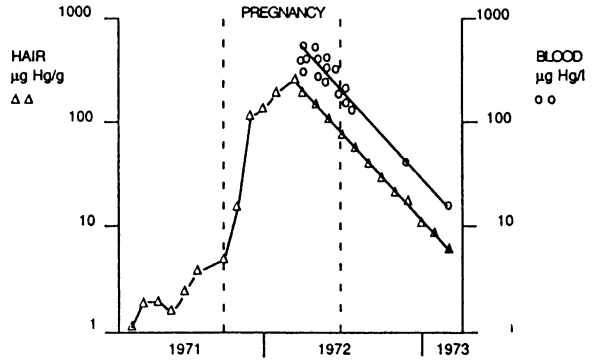

FIGURE 2. The concentrations of mercury in 1-cm segments of a sample of hair and in blood samples taken from an Iraqi mother to recapitulate exposure to methylmercury during pregnancy. The hair sample was collected in early 1973, cut close to the scalp, and divided into centimeter segments for mercury analysis. The mercury concentration in each segment was plotted according to its date of formation assuming a growth rate of 1 cm per month. Adapted from Figure 6 of Amin-Zaki et al. (*19*).

Elimination of methylmercury from the body follows first-order kinetics. As pointed out by Berglund and Berlin (*16*), this implies that methylmercury distributes within the tissue compartments at a rapid rate compared to the rate of excretion. Thus we should expect tissue concentration ratios to be steady and not subject to fluctuations due to excretion. Evans et al. (*17*) demonstrated that brain-to-blood concentration ratios were constant for any given animal species. Primates had the highest brain-to-blood ratios. Their findings confirmed those of Berlin et al. (*18*), who reported concentration ratios in the range of 5 to 1 in primates. Information on humans is sparse but is consistent with a ratio in this range (*15*).

The finding that blood levels are preditive of levels in the target organ, the brain, makes blood a valuable indicator media. However, it turns out that scalp hair is an excellent indicator of blood levels and can also recapitulate blood levels for months or even years before the collection of the hair sample. An illustration of the close parallel between blood and hair levels is given in Figure 2, which was taken from a clinical study on infant-mother pairs exposed to methylmercury in the Iraq outbreak (*19*). The mother was admitted to hospital during pregnancy and blood samples were collected and analyzed for mercury. Subsequently, a hair sample was collected, divided into centimeter segments measured from the scalp end and each segment analyzed for mercury. Hair grows at approximately 1 cm. per month. Thus it was possible to plot the mercury value in the segment according to the month the hair segment had been formed. This close parallel between hair and blood, reported in many other studies [for review, see Suzuki (*20*)], indicated that methylmercury in the hair follicle is proportional to the simultaneous blood concentration. Once incorporated into the newly formed hair, its concentration remains constant. The scalp hair sample is the indicator medium of choice as it can reveal both past and present blood concentrations and can be collected non invasively and is easily stored and transported. Hair has been widely used in our population studies in Iraq (*21*), in Peru (*22*), in American Samoa (*23*), and in Canada (*24*). These and other studies have shown that the hair-to-blood concentration ratio is about 250 to 1 (*25*).

Numerous studies have shown that the decline in blood (or hair) levels after cessation of exposure follows first-order kinetics and can be described, therefore, by a single biological half-time. Our observations on six subjects ingesting a single low dose (*14*) and on Iraqi mothers exposed for many months (*26*) yielded almost identical average half-times of about 50 days. These values are in agreement with those reported by Miettinen et al. (*13*) in young adult males taking a single oral dose of radiolabeled methyl mercury.

We now have information on all the parameters that relate long-term daily exposure to hair levels (Fig. 1). Thus it may be shown that the blood level, b (μg Hg/L) is given by the equation

$$b = df\ln 2/t_{1/2} \quad (1)$$

where d (μg Hg) is the daily ingested dose, f is the fraction that is deposited in 1L of blood, and $t^{1/2}$ (days) is the biological half-time in blood. Equation 1 holds after a steady-state body burden has been attained [for further discussion, see WHO (*25*)]. This will take a period of time equivalent to approximately five half-times. It turns out that the steady blood level when expressed in units of micrograms of mercury per liter is approximately numerically equal to the daily intake in micrograms of mercury (*25*).

Population studies in which daily intake has been measured and directly compared to blood levels indicate that the observed blood level is somewhat lower than that predicted by Equation 1. The reasons for this discrepancy are not known, but it may be that these populations were not in true steady state. Also, the estimation of daily intake in cross-sectional studies of populations is notoriously difficult.

Step 2 in Figure 1 is completed by converting the blood-to-hair level using the average value for the concentration ratio. Our studies in Iraq (*19*) and in Canada (*24*) are consistent with other reports (*25*) that, on the average, the hair concentration is about 250 times the corresponding blood level. However, considerable individual differences exist. On an individual basis, therefore, the calculations in step 2 of Figure 1 are prone to uncertainty. Ultimately, the key relationship is between hair levels and those in the brain. At this time, we do not know if the individual differences seen in hair-to-blood ratios also are reflected in hair-to-brain ratios.

Advances have been made in our understanding of the mechanisms of methylmercury transport within the body. Textbook explanations invoke the so-called lipid solubility of methylmercury. In fact, few compounds of methylmercury are soluble in nonpolar solvents. The idea of lipid solubility may have arisen because the most commonly used compund experimentally, methylmercury chloride, is, indeed, very soluble in nonpolar solvents. However, methylmercury, along with other mercuric cations, preferentially forms compounds with thiol-containing molecules. Beacuse in tissues most thiols are located in proteins, peptides, and amino acids, methylmercury has always been found as a water-soluble compound (*25*).

Thus the question arises as to how methylmercury moves so easily between tissue compartments and across major diffusion barriers such as the placenta and the blood–brain barrier. The first clue came from the finding that methylmercury is secreted into rat bile mainly as a small, water-soluble compound, ten-

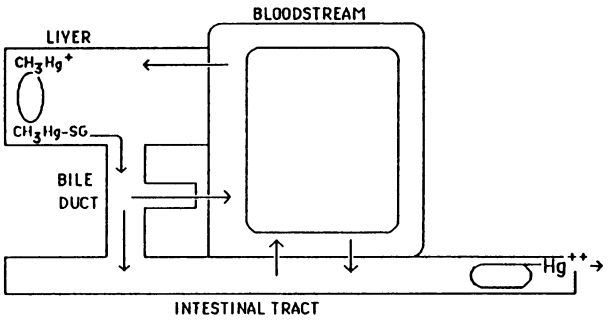

FIGURE 3. The enterohepatic recirculation of methylmercury compounds.

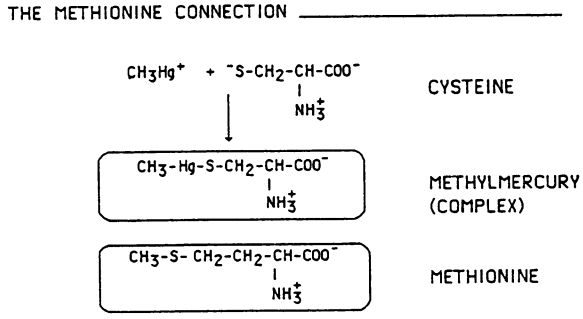

FIGURE 4. The structural similarity between the methylmercury cysteine complex and the large, neutral amino acid methionine.

tatively identified as methylmercury cysteine (*27*). Subsequently, it was shown that methylmercury glutathione was the major compound of methylmercury in bile (*28*). It now seems likely (*29,30*) that the methylmercury glutathione complex is transported out of the liver cell into the bile cannicula on the glutathione carrier (Fig. 3). The glutathione complex has been identified in the liver of animals treated with methylmercury. It may form there by purely chemical reactions, due to the high concentration of glutathione within the liver cell, or by catalysis by glutathione-*S*-transferase (GSH) enzymes (*31*). Absorption of the GSH conjugate or its mercury-containing hydrolysis products takes place in the gall bladder (*32*) and perhaps other locations in the biliary system. Further absorption takes place in the small intestine (*27*). Some secretion of mercury may also occur but the chemical compounds of mercury either reabsorbed or secreted are not yet identified.

Methylmercury remaining in the lower gastrointestinal tract is subject to demethylation to inorganic mercury. The latter is poorly absorbed and excreted in the feces. In humans the importance of the demethylation step is illustrated by the fact that all the mercury is in the inorganic form in people exposed solely to methylmercury (*33*).

The existence of an enterohepatic cycle for methylmercury led to the idea that fecal excretion could be increased if this cycle was broken by trapping methylmercury in the intestinal tract (*34,35*). Clarkson et al. (*34*) tested several types of mercury binding resins. Only the one carrying fixed -SH groups proved to be successful in enhancing methylmercury excretion in rats. Subsequently this resin was shown to reduce blood levels of methylmercury in patients in the Iraq outbreak. Takahashi and Hirayama (*35*) found that human hair, treated with reducing agents to transform keratin to kerateine, given orally to rats, was also successful in enhancing fecal excretion in these rats.

Fecal excretion, which is the predominant route of elimination of methylmercury in humans and animals, is clearly a highly complex process (Fig. 3). It is not surprising that a considerable degree of individual differences exist in excretion rates. Shahristani et al. (*36*) reported a bimodal distribution of biological half-times in people exposed to methylmercury in the Iraq outbreak. Our studies also indicated a wide range of half-time values from tless than 20 to more than 70 days (*26*). In fact, animal experiments indicated that sex, age, and genetics are important in determining individual differences in half-times (*37–40*).

Suckling animals have much lower excretion rates than mature animals (*37,38,41*). Rowland et al. (*42*) have shown that the demethylating step has a reduced activity and Ballatori and Clarkson (*43*) have reported reduced biliary secretion of methylmercury and glutathione during the suckling period. Lactation reduces the biological half-times in humans. Factors such as diet (*44*) and microflora (*45*) influence methylmercury excretion in adult animals.

The ligation of the common bile duet in rats caused a redistribution of methylmercury in the body (*27*). This finding suggested that the low molecular weight thiol complexes of methylmercury, after reabsorption from bile, played a role in transport to tissues. Thomas and Smith (*46*) and Hirayama (*47,48*) reported that methylmercury, injected into rats as a complex with the amino acid cysteine, penetrated more rapidly into the brain than other compounds of methylmercury. Recently, strong evidence has been published (*49–51*) in support of Hirayama's original suggestion that methylmercury cysteine is transported on the large neutral amino acid carrier. It was suggested that the structural similarity to the large neutral amino acid methionine is the likely explanation for transport via this carrier (Fig. 4). The enzyme γ-glutamyltranspeptidase may contribute to brain transport via hydrolysis of the glutathione complex of methylmercury in plasma to the cysteine complex (*51*).

Glutathione and cysteine complexes of methylmercury may be involved in membrane transport in other tissues. Thus, methylmercury probably enters kidney cells as the cysteine complex and exits the same cells as the glutathione complex (*52–54*). It remains to be seen if two general transport pathways exist for all mammalian cells, entry on the large neutral amino acid carrier and exit via the glutathione carrier.

Toxic Action and Dose–Response Relationships

Toxicity in Adults

The outbreaks of severe poisoning in Japan, Iraq, and elsewhere revealed important characteristics of methylmercury action in human adults (*3,55*). Overt signs and symptoms usually take weeks or months to manifest themselves. In the 1971–1972 outbreak in Iraq, for example, some victims ingested what would eventually prove to be a lethal dose without experiencing any untoward symptoms during the intake period (weeks or months). The length of this "latent" period has been shown to be inversely

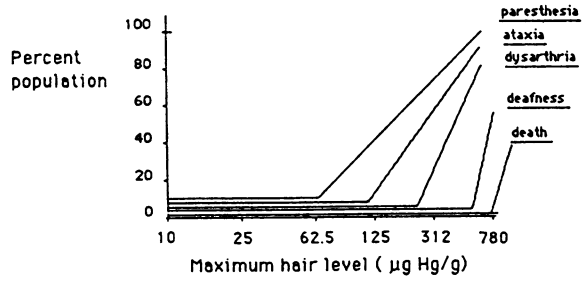

FIGURE 5. A dose-response relationship for the effects of methylmercury on adults. The percentage of the population having a specified symptom or sign is plotted against the maximum hair concentration. The hair concentration was calcultated from the body burden assuming 1% of the body burden is in 1 L of whole blood and that the hair contains 250 times the corresponding concentration in blood. Adapted from Figure 5 in Bakir et al. (*3*).

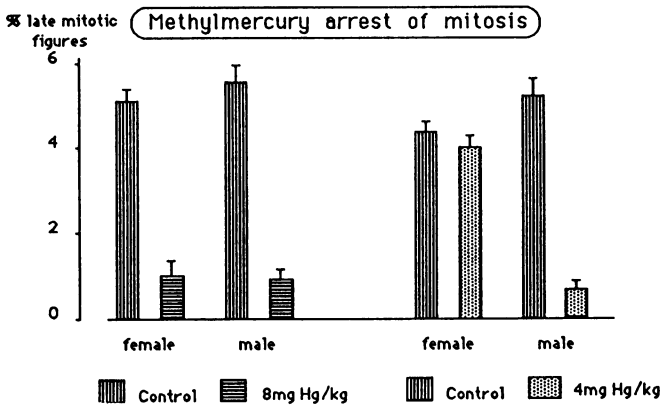

FIGURE 6. Late mitotic arrest in neurons in the developing brain due to methylmercury. Two-day-old mice were given 4 or 8 mg Hg/kg as methylmercury chloride *per os* and killed 24 hr later. The total number of mitotic figures in the external granule layer of the cerebellar cortex were recorded in matched sections and classified as early or late. The data are plotted as the percentage of late mitotic figures (anaphase or telophase). The bars are the SEs (n = 10–15). Adapted from Sager et al. (*65*).

related to the blood concentration in primates experiments (*17*).

Except at the very highest doses, all the signs and symptoms are due to selective damage to the nervous system. This property seems to be unique to methylmercury compounds at least in terms of human response. The brain is the primary target, and even within this organ, selective or focal damage is the dominant characteristic. Thus, in severe cases in Minamata as well as in animal experiments, certain anatomical areas of the brain appear to be specially susceptible to damage. These include the visual cortex and the granule layer of the cerebellum (*56*). Severe damage manifests itself as a loss of neuronal cells in these areas.

The reason for the long latent period is not known. In animals, inhibition of neuronal protein synthesis precedes the appearance of clinical effects (*57*). However, Verity and Sarafian (*58*) have questioned that inhibition of protein synthesis can itself be a direct cause of cell death.

The reason for the focal distribution of damage is also not known. Syversen (*59*) has suggested that the susceptible neurons are those incapable of repairing the initial damage inflicted by methylmercury. This is an appealing theory as methylmercury is known to be toxic to most cells types *in vitro*.

Dose-response relationships were reported in adults in our studies of the Iraq outbreak (Fig. 5). We chose to use a threshold model as it gave an excellent fit to the data and also illustrated that the more severe effects appear at higher threshold levels of methylmercury. The dose-response relationship for each effect is characterized by a horizontal segment and an inclined segment. The horizontal segment indicates a background frequency of the sign or symptom that is found in this population and is not related to methylmercury exposure. The inclined segment indicates an increase in frequency over the background level as the methylmercury levels increase. The intersection of the two lines is a practical threshold above which effects due to methylmercury become detectable. It may be seen that the threshold for paresthesia is the lowest, a finding consistent throughout most clinical and epidemiological studies of adult poisoning. The fact that the earliest effect of methylmercury is a nonspecific symptom of paresthesia makes diagnosis of incipient methylmercury poisoning very difficult. Relationships of the type depicted in Figure 5 are essential to step 3 of the risk analysis in Figure 1. However, recent studies have revealed that more relevant dose-response data come from prenatal exposure, as this stage of the life cycle is the most susceptible to methylmercury poisoning.

Prenatal Toxicity

The first indication that prenatal exposure was the most hazardous form of exposure came from reports of the Minamata outbreak (*60*). Females exposed to methylmercury during pregnancy gave birth to infants suffering from severe brain damage. The mothers experienced asymptotic or only mild effects such as transient paresthesia. Animal experiments soon confirmed the unique sensitivity of the fetus (*61*). We also noted severe cases of mental retardation early in the Iraq outbreak (*62*). However, later follow-up studies revealed a milder form of prenatal damage characterized by psychomotor retardation (*63*).

Sex differences in susceptibility were first reported in a study of prenatally exposed Canadian Indians. McKeown-Eyssen et al. (*64*) were first to report that males were more affected than females. An examination of the cases in Iraq confirmed that more severe effects were seen in male infants (*21*). Animal experiments also found the effects on cell division were more pronounced in males (Fig. 6). In these experiments (*65*), neonatal mice were given a single dose of methylmercury, and effects on the dividing cells of the granule layer of the cerebellum were recorded. At the higher dose, 8 mg Hg/kg, both male and female animals showed delayed mitotic arrest, but at the lower dose, 4 mg Hg/kg, only the males showed this effect.

The nature of prenatal damage appears to differ fundamentally from that of adult damage to the central nervous system [for review, see Choi (*66*)]. Unlike focal damage in adults, damage to the developing brain is diffuse and widespread. In severe cases, ectopic neurons are seen, suggesting that methylmercury has interfered with neuronal migration (*67*). Microcephaly suggests that cell division has been suppressed. As discussed above, animal experiments confirmed that methylmercury can cause late mitotic arrest of neuronal cells (Fig. 6).

Methylmercury has been shown both *in vitro* and *in vivo* to

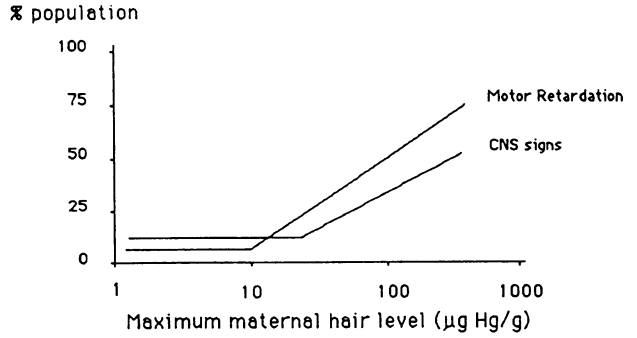

FIGURE 7. Dose-response relationships for prenatal exposure to methylmercury. The percentage of infants exhibiting delayed motor development or abnormal reflexes are plotted against the maximum maternal hair concentration during pregnancy. Adapted from Cox et al. (*26*).

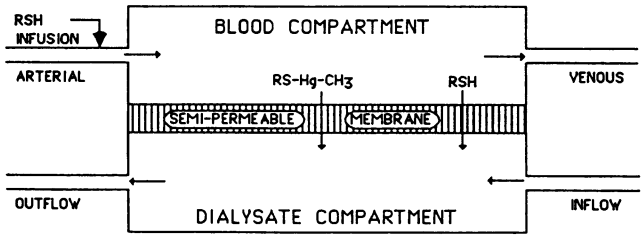

FIGURE 8. The principle behind the use of extracorporeal complexation hemodialysis to remove methylmercury from the bloodstream. Adapted from Kostyniak et al. (*71*).

depolymerize microtubules (*68*). Microtubules are the first subcellular structure to be affected at the lowest concentrations of methylmercury (*69*). Microtubules play an essential role in both cell division and in neuronal migration. Thus methylmercury is damaging that component of neuronal cells that is essential for two basic processes in the developing brain cell division and cell migration.

Quantitative information on the greater susceptibility of the fetus became available in our follow-up studies of the Iraq outbreak (*21,26,63*). Two of these relationships are depicted in Figure 7. We used the same threshold model as in the adult study to allow a direct comparison of adult and prenatal exposures. Whereas the practical threshold in the adult dose resronse was in the range of 50–100 μg Hg/g har, the prenatal threshold was in the range of 10–20 μg Hg/g hair. Despite the uncertainties in the estimates of these threshold values, these dose-response data indicated that the fetus may be 5–10 times more sensitive than the adult to brain damage from methylmercury. Thus, prenatal dose-response relationships are the ones most relevant to human risk assessment and to step 3 of Figure 1.

More studies are needed as the data from Iraq were limited to only about 80 infant mother pairs. Moreover, exposure today to methylmercury is through fish, wheras in Iraq methylmercury was consumed in contaminated fish.

Treatment of Methylmercury Poisoning

In its severe form, methylmercury poisoning is essentially irreversible due to the destruction of neuronal cells (*56*). Thus, treatment is directed toward early removal of methylmercury from the body before irreversible damage occurs to prevent further damage. Only complexing or chelating agents that contain-SH ligands are effective. Thus, D-penicillamine and *N*-acetyl-D-penicillamine were shown to be effective in reducing blood levels in the Iraq outbreak (*70*). The use of an-SH-containing resin has already been described in the discussion of the enterohepatic circulation of methylmercury.

A novel method involving hemodialysis was developed for treatment of patients in Iraq (Fig. 8). Methylmercury is present in blood bound mainly to red blood cells and to plasma proteins (*71*). Only trace amounts are in the form of diffusible molecules. Thus, the normal hemodialysis procedure removes little methylmercury from blood (*71*). However, if a diffusible thiol compound such as the amino acid cysteine is introduced into the arterial circuit, a fraction of the methylmercury in blood is converted to a diffusible form that can be removed by dialysis. The procedure was first shown to be highly effective in experimental animals (*72*) and subsequently applied to reducing blood levels in Iraqi patients (*73*). The method has subsequently been used in a case of acute methylmercury exposure in the United States (*74*).

Today two dithiol complexing agents, dimercartosuccinic acid and dimercaptopropane sulfonate, show promise as surperior agents to the traditional ones now in use (*75*). Dimercaptosuccinic acid has been more extensively investigated for removal of methylmercury from the body (*76,77*). Dimercatosuccinic acid also may be the complexing agent of chioce in the hemodialysis procedure (*78*).

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